Diseases of Laboratory Rabbits

*Oryctolagus cuniculus*

Timothy K Cooper DVM, PhD, DACVP

**Disclosure**

I am presently employed by Charles River Laboratories as a contractor pathologist supporting NIAID-IRF (NIH)

The opinions expressed are my own and not sponsored by either entity.

This lecture is outside of and unrelated to my duties at CRL or NIAID

**Acknowledgements**

Dr. James W Griffith
Dr. Bruce Williams
Dr. Jo Lynn Raymond
Various other contributors

Numerous laboratory animal medicine residents (PSUHMC)

**European Rabbits (Oryctolagus cuniculus)**

*Order Lagomorpha, family Leporidae*

- Descendants of the European wild rabbit (Old world rabbit)
- Domesticated in France circa 500 AD
- Over 100 different breeds
  - New Zealand White (NZW) and Dutch Belted most common (outbred stock)
  - Inbred strains exist (e.g. Audiogenic (EIII/JC))

**New World Rabbits**

*Order Lagomorpha, family Leporidae*

- Eastern cottontail (*Sylvilagus floridanus*)
- Swamp rabbit (*S. aquaticus*)
- Marsh rabbit (*S. palustris*)
  - And many others

INHAND for Non-Rodents in development

[https://www.toxpath.org/inhand.asp](https://www.toxpath.org/inhand.asp)
NORMAL ANATOMY AND BIOLOGY

Cardiovascular System

- Chambers on right side are thin
- Clotted blood common in the right ventricle without any evidence of contraction
- The right atrioventricular (tricuspid) valve is bicuspid
- Like dogs and pigs, there are only two branches from the aortic arch:
  - Brachiocephalic trunk (innominate artery)
    - Right subclavian
    - Right common carotid
    - Left common carotid
  - Left subclavian artery

Cardiovascular System (NZW)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Reference interval (non-parametric)</th>
<th>90% CI</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>HW</td>
<td>8.74</td>
<td>3.64-15.35</td>
<td>3.20-4.75</td>
<td>85</td>
</tr>
<tr>
<td>HW:BW*</td>
<td>0.26</td>
<td>0.13-0.45</td>
<td>0.11-0.17</td>
<td>92</td>
</tr>
<tr>
<td>HW:BSA</td>
<td>0.38</td>
<td>0.21-0.68</td>
<td>0.19-0.28</td>
<td>89</td>
</tr>
<tr>
<td>(LVFW+IVS)</td>
<td>3.66</td>
<td>2.64-4.73</td>
<td>2.60-2.93</td>
<td>59</td>
</tr>
<tr>
<td>RVFW</td>
<td></td>
<td></td>
<td>4.48-4.77</td>
<td></td>
</tr>
</tbody>
</table>

*=Rabbit heart is relatively small

By comparison, mean HW and HW:BW for domestic cat is 17.2 and 0.40 (PMID 26776590)

Respiratory System

- Like mice, rabbits are obligate nasal breathers
- Relatively narrow trachea and small thorax
- Unlike rodents, left lung is subdivided into 3 lobes
- No respiratory bronchioles

Prominent marginal ear veins
Euthanasia Solution Artifact

Gastrointestinal System

- Additional pair of incisors (peg teeth) directly behind the maxillary incisors
- Dental formula: 
  \[(I2/1, C0/0, PM3/2, M2-3/3) \times 2 = 26 \text{ or } 28\]
- Diphyodont (deciduous and adult sets of teeth)
- All teeth grow continuously (elodont)

Gastrointestinal System

- Rapid gut transit time
- Feed early morning and evening and at night (crepuscular)
- Do not vomit (cardiac sphincter)

Gastrointestinal System

- No non-glandular stomach
- Hindgut fermenters (40% ingesta in cecum)
- GI tract long, contents are 10-20% of body weight
- Abundant gut-associated lymphoid tissue, makes up ≥50% of the lymphoid mass (sacculus rotundus (ileocecal junction), cecal tonsil, and appendix)
- Calcium absorption not regulated by vitamin D

Published in: Susan A. Elmore; et al. Proceedings of the 2018 National Toxicology Program Satellite Symposium Toxicol Pathol. DOI: 10.1177/0192623318800734 Copyright © 2018 Society of Toxicologic Pathology
POOP

- Day (hard) feces – hard fecal pellets containing mostly undigestible fiber
- Night (soft) feces – from cecal content (cecotrophs), covered with mucinous coat, rich with vitamins, proteins and electrolytes, swallowed directly by rabbits while defecating (coprophagia)  

Cecotrophy under control of the fusus coli located at the junction between the transverse and descending colon

Urinary Tract

- Kidneys are unipapillate
- Insensitive to loop diuretics (e.g. furosemide)
- Urine is the major route of calcium and magnesium excretion (FE\textsubscript{Ca}=45\% (versus 2\% in other species))
- Urine contains many crystals which forms a thick sediment
- Normal urine color can vary from yellow to red (porphyrins and urobilinogen)
- pH>8.0
Reproductive Tract

- Females are does; males are bucks
- Puberty at 4-6 months
- Breeding lifespan is 3-4 years
- Induced ovulators (10-13 hours post-coitus)
  – Pseudopregnancy is common
- Discoid labyrinthine hemochorial placentation
- Gestation 31-32 days, 4-10 kits
- 4-7 litters per year

Uterus Duplex

- Uterus lacks a body
- Two separate uterine horns (bicornuate)
- Two separate cervixes open into vagina (duplex)

Vaginal mucosa mostly simple columnar except near vulva

Hemolymphatic System

- Blood volume 55.6 ml/kg (44-70 ml/kg)
- Polychromasia normal
- Erythrocyte lifespan 50d.
- Lymphocytes are predominant circulating leukocyte
- May have large numbers of circulating basophils
- Often respond to acute infections with neutrophilia (heterophilia) and lymphopenia, with a normal leukocyte count

Prominent Ovarian Interstitial Glands
**Hemolymphatic System**

- Antibodies are high affinity, including to poorly antigenic substances (e.g. carbohydrates)
- B cell lymphopoiesis in the bone marrow ends by 2 to 4 months of age
  - Minimal B lymphopoiesis in adult spleen
- Appendix is the major site of B cell somatic diversification
  - Dependence on flora; germfree rabbits are immunocompromised
- No IgD; >10 IgA subtypes
- Predominantly (70-90%) a single V\_H segment (V\_H\_1)
- Numerous kappa light chain V\_K and J\_K segments

**Heterophils**

- Major circulating granulocyte
- Stain intensely, similar to avian or reptilian heterophils
- Functionally equivalent to neutrophils, i.e. rabbits can and readily do suppurate

**Ectopic (Daughter) Spleens Common**

**VIRUSES**

**Rabbit Hemorrhagic Disease Virus**

- Type species of Lagovirus, Caliciviridae
- Young animals (<4-8 weeks) resistant to clinical disease
- Transmission by direct contact and contaminated fomites, including arthropods
- Virus is highly resistant to inactivation
- Recovered animals may shed the virus for one month
- Sylvilagus spp. are resistant, so there is no wildlife reservoir in the US
- Morbidity is 30-100% with 40-100% mortality

FOREIGN ANIMAL DISEASE, REPORTABLE TO USDA/APHIS

**Viral Taxonomy**

- Order: Herpesvirales
  - Family: Herpesviridae
- Subfamily: Alphaherpesvirinae
  - Genus: Simplexvirus
    » Species: Macacine alphaherpesvirus-1
- Member: herpes virus B (or B virus or monkey B virus)

https://talk.ictvonline.org/taxonomy
Novel Rabbit Calicivirus (Michigan)

- Single outbreak in 2001 with 32.5% mortality
- 79% genomic similarity with RHD virus
- Could not induce experimental disease

Myxomatosis

- **Myxoma virus**
- Type species of *Leporipoxvirus, Poxviridae*
- Transmission by direct contact and arthropods
- Enzootic in *Sylvilagus* rabbits of North and South America
  - Asymptomatic reservoir for infection of domestic rabbits
  - *S. bachmani* on Pacific coast (CA and OR)

**FOREIGN ANIMAL DISEASE, REPORTABLE TO USDA/APHIS**

Shope Fibroma

- **Rabbit fibroma virus**
- *Leporipoxvirus, Poxviridae*
- Transmission by direct contact and arthropods
- Enzootic in *Sylvilagus* rabbits
- SQ nodules on head and legs
- Lesions spontaneously regress

Stellate cells with intracytoplasmic inclusion bodies in a loose (myxomatous) collagenous matrix with inflammatory cells

Richard E. Shope MD 1931-1966
Rabbit Pox

- Unclassified Orthopoxvirus
- Only laboratory outbreaks reported
- Aerosol spread
- Possibly derived from vaccinia
- Used as a model for smallpox (variola)

Leporid Herpesvirus-4

- Herpesviridae, Alphaherpesvirinae, Simplexvirus, Leporid alphaherpesvirus-4
- Outbreaks in Canada and Alaska in rabbits housed outside
- Clinically resembled myxomatosis
- Ocular and anogenital skin necrosis with lymphoid necrosis (spleen)
- Pulmonary and GI hemorrhage
- Herpetic intranuclear inclusion bodies + syncytial cells

**Herpes Simplex**

- *Human alphaherpes 1 and 2*
- Reverse zoonosis (anthroponosis)
- Rabbits extremely sensitive to infection
- Necrotizing meningoencephalitis
- Inclusions in neurons and astroglial cells

**Shope Papilloma**

- Sylvilagus floridanus papillomavirus 1
- aka cottontail rabbit papillomavirus (CRPV)
- Endemic in *Sylvilagus* rabbits

*Oryctolagus* can be experimentally infected by scarification as a model for human cutaneous and genital papillomavirus

---

**Oral Papillomatosis**

- *Oryctolagus cuniculus papillomavirus-1 (OcPV1)*
- White, fleshy, exophytic masses along the ventral margin of the tongue
- Spread by direct contact in areas with mucosal damage
- Self-limiting
Other Viruses

- Rotavirus A
- Coronavirus
  - Enterotropic
  - Cardiotropic (pleural effusion disease)
- Hepatitis E virus (Orthohepevirus A, potential zoonosis)
- Astrovirus
- Adenovirus (Europe)
- Bornavirus (mammalian Orthobornavirus, Europe)
- Lapine parvovirus (Japan)

Rabies

- 49 cases in US (1979-2010)
- Pet rabbits housed outdoors

Rabbits are an important experimental model for rabies
- Pasteur originally attenuated the rabies virus for vaccination by serial passage through rabbits

Apathogenic Viruses

- Herpes cuniculi or virus III (Leporid herpesvirus-2)
- Cottontail rabbit herpes (Leporid herpesvirus-1)
- Herpes sylvilagus (Leporid herpesvirus-3)
- Rabbit kidney vacuolating virus (Polyomavirus)
- Sendai virus (Murine respirovirus, Paramyxoviridae)

BACTERIA

Pasteurellosis aka “Snuffles”

- Pasteurella multocida subspecies multocida capsular type A or D
- Type A is the single most common isolate

Culture of deep nasal swabs as part of test and cull strategy
  - 70% sensitivity
  - 100% specificity
If you see pus anywhere in a rabbit, *Pasteurella multocida* should be at or near the top of your differential etiology list.
Genital Tract

- Pyometra
- Metritis
- Salpingitis
- Oophoritis
- Orchitis

Bordetellosis

- *Bordetella bronchiseptica*
- Opportunistic respiratory tract pathogen
- More indolent disease than *Pasteurellosis*
- Can cause clinical pneumonia in weaned kits (often with concurrent pneumocystosis)
**Staphylococcus aureus**

Can be normal oral and skin flora
- Blue bag gangrenous mastitis
- Abscesses (esp. SQ)
- Pododermatitis
- Generalized infection/septicemia in nursing kits

Can clinically resemble Pasteurellosis

---

**Diarrhea in Rabbits**

- Rotavirus (A)
- Enteric coronavirus
- *Clostridium spiroforme*
  - *C. difficile*
  - *C. perfringens*
  - *C. piliforme*
- Enteropathogenic *E. coli*
- Enterohemorrhagic *E. coli*

- *Lawsonia intracellularis*
- Coccidia, esp. highly pathogenic
  - *Eimeria intestinalis*
  - *E. flavescens*
- *Salmonella sp.*
- *Yersinia pseudotuberculosis, Y. enterocolitica*

---

**Clostridial Typhlocolitis**

- *Clostridium spiroforme*
  - Iota toxin
- *C. difficile*
- *C. perfringens*

Opportunistic pathogens following disruption of normal flora (dysbiosis)
Diagnosis of these agents is NOT by culture
Must demonstrate toxin production
Tyzzer’s Disease

Clostridium piliforme

- Cecum
- Liver
- Heart

Ernest Edward Tyzzer MD
**Proliferative Enteropathy**

*Lawsonia intracellularis*

- Obligate intracellular bacteria
- Suckling, weanling and adults
- Mostly acute
- Ileum, cecum, colon
- Three forms:
  - Erosive
  - Suppurative
  - Proliferative


Warthin-Starry
Blue Fur Disease
• Moist dermatitis due to *Pseudomonas aeruginosa*
• Pyocyanin produced by bacteria discolors fur

Rabbit Syphilis
• *Treponema paraluisncuniculi* (*T. cuniculi*)
• Benign venereal infection with no systemic spread (unlike human syphilis, *T. pallidum*)

NOT ZOONOTIC
Bacterial Septicemias

- Tularemia
  - *Francisella tularensis* (Reportable)
- Salmonellosis
- Yersiniosis
  - *Yersinia pseudotuberculosis, Y. enterocolitica*
- Plague
  - *Yersinia pestis* (Reportable)

Other Bacteria

- *Escherichia coli*
  - EPEC  
  - EHEC
- *Klebsiella pneumoniae*
- *Listeria monocytogenes*
- *Fusobacterium necrophorum* 
  (Schmorl's disease)

Mycobacteriosis

- Rabbits are an excellent experimental model of pulmonary tuberculosis
- Wild *O. cuniculus* are a reservoir of *M. avium* subspecies *paratuberculosis* (Johne’s) in Scotland
- Pulmonary granulomas can result from use of complete Freund’s adjuvant (CFA)